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Mortality Following Radiation Treatment for Infertility of Hormonal Origin or Amenorrhea

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Background. Between 1920 and 1965, radiation treatment to the ovaries and/or pituitary gland was used for refractory hormonal infertility and amenorrhea. The potential carcinogenic effects of hormonal infertility, as well as exposure to relatively low doses of ovarian and pituitary radiation can be studied among patients receiving these treatments.

Methods. A cohortof 816 patients treated between 1925 and 1961 was identified from the medical records of a New York City radiologist. The mortality experience for 84% of these women was determined and radiation doses for individual patients were estimated. Doses were, on average, 87, 64, 54, and 29 cGy to the ovary, brain, colon, and active bone marrow, respectively.

Results. Compared with mortality rates in the US population, the risk of death was less than expected (standardized mortality ratio [SMR] = 0.87; 95% confidence interval [Cl] : 0.75–1.00). Deaths due to circulatory and digestive diseases were significantly below expectation. Cancer mortality was about 10% higher than that expected based on New York City mortality rates. Based on a small number of cases, no increase was found for cancers of the ovary or brain, or leukaemia, sites for which direct radiation exposure occurred, but significant excesses of colon cancer and non-Hodgkin's lymphoma were observed. A deficit in mortality from female genital cancers was surprising, since nulliparity has been a consistently reported risk factor for cancers of the endometrium and ovary. Breast cancer mortality was close to expectation.

Conclusions. Overall, this study provided little evidence that either infertility or its treatment with radiation increased the risk of total or cancer mortality.

Between 1920 and 1965, irradiation of the ovaries and/or pituitary gland was one of the treatments used for refractory hormonal infertility and amenorrhea.[1–5] This technique was described as being therapeutically valuable, harmless to the treated women, and unrelated to genetic effects. By the mid 1950s, it was estimated that approximately 2000–3000 women gave birth to children after such treatment in the US.[6] Dr Ira Kaplan, a radiologist in New York City (NYC) was a pioneer in this field and treated close to 900 women over several decades. His patients provide a unique opportunity to evaluate the carcinogenic effects of hormonal infertility, as well as exposure to relatively low doses of ovarian and pituitary radiation.

Endogenous hormones and reproductive behaviour are believed to play a major role in the development of hormone-dependent cancers. Nulliparous women are known to have elevated risks of cancers of the breast,[7] ovary,[8] and endometrium[9] and possibly colon,[10] but the biological mechanism for these associations remains unclear. Four prospective studies of cancer occurring among infertile women have been published[11–14] but the results are not entirely consistent. The studies suggest that women with fertility problems do not have an increased risk of cancer incidence when all sites are combined, but there is some evidence of an elevated risk of endometrial cancer, particularly among women with infertility of hormonal origin. Results regarding cancers of the breast and ovary are inconclusive. In a recent collaborative analysis of ovarian cancer case-control studies, three provided self-reported information on type of infertility and fertility drug usage. Based on 14 exposed cases and 1 exposed control, fertility drug usage was associated with an increased risk of ovarian cancer among nulligravid women.[8] The long-term effects of infertility or its treatment have not been studied in terms of non-cancer diseases.

Radiation is a well documented carcinogen, and studies of populations exposed medically or accidentally

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TABLE 1 *Selected characteristics of women treated with radiation for infertility of hormonal origin or amenorrhea*

Number of patients identified	872
Exclusions:	
foreign	46
no treatment record	5
insufficient information for follow-up	5
Total patients analysed	816
Average age at entry, years (range)	28.8 (15–48)
Average year of entry (range)	1946.8 (1922–1961)
Average age at death, years (range)	66.0 (26–93)
Average year at death (range)	1977.1 (1933–1990)
Woman-years of observation (average)	28 438 (34.8)
Vital status as of 1 January 1991	
alive (%)	486 (59.6%)
dead (%)	199 (24.4%)
lost to follow-up (%)	131 (16.0%)

have shown that radiation can induce cancer in most organs.[15,16] The women treated with the Kaplan technique are of interest because they were exposed to relatively low doses of partial body radiation; approximately 90 cGy to the ovaries and 65 cGy to the brain. Because these patients were irradiated many decades ago, the long-term effects of this radiation can now be studied.

METHODS

Study Cohort

The study cohort consists of women with hormonal infertility treated with radiation by Dr Ira Kaplan between 1925 and 1961. These patients had all been referred by other physicians, usually gynecologists, because they had failed to respond to other modes of treatment. Upon his death, Dr Kaplan left his medical records to the US government so that his patients and their children could be followed to evaluate the late consequences of gonadal irradiation. These records were abstracted to obtain personal identification and location data, and information on infertility, medical history, examination at initial visit, radiation treatments and treatment outcome. Out of a total of 872 patients who met the study criteria, 816 were included in the final study cohort. Patients were excluded from the study for the following reasons: 46 lived outside of the US; data required for follow-up were not available for five; and treatment records were not found for another five (Table 1).

Radiation Treatment

Most women had radiation treatment to their ovaries and pituitary gland; 48 patients received ovarian radiation only; four women received treatment solely to their pituitary gland; and for one patient the record was not clear. Treatments were quite uniform and typically were delivered with an orthovoltage x-ray unit operating at 200 kVp, with a 1.0 mm Cu half-value layer (HVL), and a skin target distance ranging from 30 to 50 cm. Pelvic treatment fields were 8 by 10 cm, right and left, anterior and posterior. A round anterior field, 5 cm in diameter, was used to irradiate the pituitary. A course of therapy consisted of three treatments delivered at intervals of 7 days. The total exposure in air for the pelvic fields was 100 roentgen to each of the anterior fields and 76 to each of the posterior fields. The pituitary field received 225 roentgen. Ninety-six patients had more than one therapy course. Thirty-two women did not receive the full three-treatment course of therapy.

TABLE 2 *Mean organ doses from x-ray treatment for infertility of hormonal origin or amenorrhea*

Organ	Dose in cGy			
	Mean	Standard deviation	Median	5th–95th percentile
Ovary	87.5	29.1	76	65–150
Brain	64.0	27.5	62	0.1–120
Uterus	54.4	23.0	44	37–90
Colon, average[a]	54.0	19.9	45	39–90
Sigmoid	101.8	34.1	89	76–180
Total active bone marrow[b]	29.2	10.0	25	22–50
Pelvis	61.8	22.2	52	46–100
Thyroid	3.4	34.9	0.8	0.2–1.7
Breast	1.1	5.2	0.7	0.6–1.3

[a] The average colon dose was calculated as a weighted average of the doses to the ascending, descending, transverse, and sigmoid segments.

[b] As described in Stovall *et al.* [18] the dose to the total active bone marrow was calculated as a weighted average of the dose to each of 14 skeletal compartments. Data from Christy[17] were used to estimate the active bone marrow in each component.

Dosimetry

Copies of each patient's radiotherapy records were sent to medical physicists at the University of Texas MD Anderson Cancer Center for estimation of dose to sites of interest. A quality score was assigned to indicate the level of information in each patient's record. The records were inadequate to estimate doses for 12 treatments. For 134 patients, the records described administered doses in terms of per cent skin erythema dose (% SED), a measure of skin reaction used in the 1920s and 1930s. Although the quality of the exposure information based on % SED is not optimal, it was considered sufficient to estimate organ doses.

To estimate doses to sites of interest, measurements in a water phantom were incorporated into a mathematical computer model simulating an adult female. Several hundred points of calculation allowed an estimation of average and range of dose for each organ of interest. Organ doses were calculated for each individual in the study, based on her treatment parameters. Because doses varied widely in the colon, in addition to an average dose, doses were determined for seven separate parts (i.e. caecum, sigmoid, ascending, descending, and transverse colon, and the hepatic and splenic flexures). Bone marrow doses were calculated for 14 anatomical sites based on the estimated amount of bone marrow at each site.[17,18]

Table 2 provides the average and median doses to selected organs. The same treatment regimen was used for the majority of patients and, therefore, the range of doses was fairly limited. Typically the larger doses were due to multiple treatments. Only the ovary, brain, and sigmoid colon received a median dose of more than 50 cGy. The sigmoid dose is about 20% greater than the dose to the ovaries because the ovaries are about equidistant to the posterior and anterior fields, whereas the sigmoid is closer to the posterior field.

Follow-up

To trace this study cohort, a comprehensive effort involving a large variety of public and private sources was needed. In addition, community and private organizations were contacted when necessary and a private company, which specializes in locating people in NYC, was also employed. If it was not clear whether the correct person had been located, the study subject was contacted directly.

As of 1 January 1991, vital status was known for 84% of the study cohort (Table 1). The mean length of follow-up was 35 years, with 42% of the study subjects having more than 40 years of observation and only 12% having less than 10 years of follow-up. Death certificates were obtained for all but two of the deceased study subjects. The underlying cause of death was coded by a nosologist according to the International Classification of Disease (ICD),[19] Eighth Revision. Death certificates were recoded for 100% verification.

Statistical Analysis

Statistical analyses employed either US national or NYC mortality rates as an external standard for comparison. Because NYC mortality data were not available for non-cancer causes of death for all years studied, US national rates were used for non-cancer mortality analyses and NYC rates were used for type-specific cancer mortality analyses. Woman-years at risk were computed for each patient from the date of first radiation treatment until the date of death, the date last known to be alive for those lost to follow-up, or the end of follow-up (31 December 1990) for those known to be alive. Standardized mortality ratios (SMR) (the ratio of observed to expected number of deaths) were computed assuming a Poisson distribution for the observed frequency. Cause-specific expected numbers of deaths were calculated by applying the age, race, and calendar-year specific mortality rates to the appropriate woman-years at risk. The US death rates from 1925 through 1986 and NYC rates from 1950 through 1986 were used for these calculations. Death rates for 1987 through 1990 were extrapolated using an average of the 1984–1986 rates. A modified version of Monon's computer program was used to perform these calculations.[20] Dose-response analyses for specific cancer causes of death were based on the estimated dose for the closest or most appropriate organ. Because there was a standard treatment protocol, the dose distribution was narrow. For about 60% of the study population, the calculated organ-specific dose estimates were the same. We therefore categorized the doses into three groups, with the lowest dose category including the patients with the standard treatment, along with the patients receiving smaller doses (altogether about 65% of the patients). The cut-points for the medium and high dose categories were made so that the number of woman-years was similar.

RESULTS

The 816 women in the study cohort contributed 28 438 years of observation (mean = 34.8 years) (Table 1). Almost 90% of the patients were treated for infertility and 10% for amenorrhea. Among the infertile patients, 78% had never conceived (primary infertility), and 20% had infertility problems following a previous pregnancy (secondary infertility): 11% following a pregnancy loss, and 9% following a live birth. The average age at treatment was 28.8 years and the mean year of treatment was 1947.

Altogether 199 deaths were identified during the study period. The first death occurred in 1933, and the mean age at death was 66 years. An equal number of deaths (n = 79) due to cancer and circulatory diseases occurred. Each of these categories accounted for 40% of the total deaths. Eight deaths occurred during the first 10 years of observation, l4 between 10–19 years, 31 between 20–29, 75 between 30–39, and 71 between 40 and 64 years. Based on national death rates, 229.4 deaths were expected among the study subjects (Table 3). The SMR for total mortality was 0.87 (95%

TABLE 3 *Observed and expected number of deaths and standardized mortality ratios (SMR) among women treated with radiation for infertility of hormonal origin or amenorrhoea* [a]

ICD-8 codes	Cause of death	Observed	Expected[a]	SMR[a]	95% CI
0–999	All causes	199[b]	229.4	0.87	0.75–1.00
140–209	All cancers	79	65.6	1.21	0.95–1.50
0–139,240–999	All non-neoplastic causes	120	163.9	0.73	0.61–0.88
240–279	Allergy, endocrine, metabolic, nutritional	7	6.5	1.08	0.43–2.22
250	Diabetes	7	5.5	1.28	0.51–2.64
390–458	All circulatory diseases	79	102.3	0.77	0.61–0.96
410–414	Arteriosclerotic heart disease	51	59.0	0.86	0.64–1.14
430–438	Vascular lesions of the CNS	17	19.8	0.86	0.50–1.37
460–519	All respiratory diseases	14	13.0	1.08	0.59–1.81
480–486	Pneumonia	10	5.5	1.83	0.88–3.36
520–577	All diseases of the digestive system	3	10.6	0.28	0.06–0.83
571	Cirrhosis of the liver	0	4.4	0.00	0.00–0.84
800–998	All external causes	5	10.5	0.47	0.15–1.11
	All other and non-specific causes	12	20.9	0.57	0.30–1.00

[a] Expected number of deaths and SMR computed based on US national mortality rates for white women, 1925–1990.
[b] Includes two deaths for which the cause of death was unknown. These deaths are included in the 'all other and non-specific causes' category.

confidence interval [CI] : 0.75–1.00. The SMR (0.62; 95% CI : 0.39–0.94) was particularly low during the first 20 years of follow-up.

No significantly increased SMR for any broad ICD category was observed. For all malignancies there was a 20% increase in mortality, but the lower 95% CI was below unity. A significant deficit of non-cancer mortality was demonstrated (SMR = 0.73; 95% CI : 0.61–0.88). Mortality was significantly decreased for diseases of the circulatory (SMR = 0.77; 95% CI : 0.61–0.96) and digestive systems (SMR = 0.28; 95% CI : 0.06–0.83). Within the circulatory disease category, the SMR was 0.86 for both arteriosclerotic heart disease and all vascular lesions of the central nervous system. No deaths from cirrhosis of the liver were observed, although 4.4 were expected.

From 1950 on, we were able to obtain cause-specific cancer mortality data for NYC. Since the large majority of women in this cohort were originally from the New York metropolitan area and many (approximately 60%) still lived there at the end of follow-up, we felt that these rates represented a more appropriate comparison. We compared the expected number of deaths based on US national or NYC mortality rates and found that, indeed, NYC rates resulted in larger expected values for almost all causes of death. The ratio of the number of expected cancer deaths based on US compared with NYC rates mortality was 0.91 when data from 1950 to 1990 were used, and was 0.94 using rates from 1970 to 1990 (Table 4). From 1970, we also had data on non-cancer mortality from NYC and the comparable ratio of US to NYC-based expected values was 0.94 for total deaths, 0.86 for diseases of the circulatory system and 1.03 for digestive diseases. Thus, it would appear that the decreased risk of circulatory diseases may actually be somewhat more pronounced than shown in Table 3. In contrast, the SMR for digestive diseases could be slightly larger than 0.28.

TABLE 4 *Ratios of number of deaths expected to occur based on US national mortality rates compared with New York City (NYC) rates*

Cause of death	Ratio of number of deaths expected to occur between 1950 and 1990 US/NYC	Ratio of number of deaths expected to occur between 1970 and 1990 US/NYC
All causes	data not available	0.94
All cancers	0.91	0.94
Digestive cancers	0.82	0.85
Colon cancer	0.87	0.89
Respiratory cancers	1.04	1.08
Breast cancer	0.81	0.84
Ovary + other female genital cancers	0.89	0.95
Haematological malignancies	0.94	0.97
Circulatory diseases	data not available	0.86
Digestive diseases	data not available	1.03

Using the NYC mortality rates from 1950 to 1990 provided a closer comparison population, but resulted

TABLE 5 *Observed (Obs.) number of cancer deaths and standardized mortality ratios (SMR) for selected cancers stratified by time since first treatment* [a]

Cancer site	Years since treatment 0–19		20–29		30–39		40–64		Total		
	Obs.	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR	95% CI
All cancers	6	0.6	19	1.0	33	1.3	20	1.2	78	1.1	0.9–1.4
Digestive cancers	4	2.1	5	1.2	9	1.3	9	1.6	27	1.4	1.0–2.1
Oesophagus	0	0.0	0	0.0	1	3.6	1	5.2	2	2.8	0.3–10.1
Stomach	1	2.9	0	0.0	1	1.1	0	0.0	2	0.8	0.1–2.8
Colon	1	1.3	1	0.6	5	1.7	8	3.2[b]	15	1.9	1.1–3.1
Rectum	1	3.5	2	4.4	0	0.0	0	0.0	3	1.7	0.4–5.1
Liver	0	0.0	1	2.7	0	0.0	0	0.0	1	0.6	0.0–3.6
Pancreas	1	4.0	1	1.4	2	1.4	0	0.0	4	1.1	0.3–2.9
Respiratory	0	0.0	2	0.9	6	1.5	2	0.9	10	1.1	0.5–2.0
Breast	1	0.3	7	1.4	8	1.5	2	0.7	18	1.1	0.6–1.7
Uterine cervix	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0.0–1.9
Corpus uteri	0	0.0	0	0.0	1	1.4	0	0.0	1	0.6	0.0–3.5
Ovary[c]	0	0.0	1	0.6	0	0.0	2	2.1	3	0.6	0.1–1.7
Brain and other CNS	0	0.0	0	0.0	1	2.0	0	0.0	1	0.7	0.0–3.9
Non-Hodgkin's lymphoma	1	3.2	0	0.0	2	2.7	3	5.2[b]	6	2.8	1.0–6.1
Multiple myeloma	0	0.0	0	0.0	1	2.9	0	0.0	1	1.2	0.0–6.7
Leukaemia	0	0.0	0	0.0	1	1.4	1	1.8	2	0.9	0.1–3.4
Other cancers	0	0.0	4	1.8	4	1.2	1	0.4	9	1.0	0.4–1.9

[a] Expected number of deaths and SMR computed based on New York City mortality rates for white females, 1950–1990.
[b] Lower confidence limit is above 1.0.
[c] Includes 'other and unspecified female genital organs'.

in the exclusion of 61 study subjects whose follow-up ended before 1950. Among these patients there was one cancer death. Based on NYC rates, 78 cancer deaths were observed compared with 69.8 expected, yielding an SMR of 1.12 (Table 5). Deaths due to colon cancer and non-Hodgkin's lymphoma (NHL) were significantly elevated compared with the NYC general population. For both colon cancer and NHL, the SMR were highest 40 years after treatment. The SMR for respiratory and breast cancers were close to what would be expected, and the SMR for cancers of the cervix, endometrium and ovary and other female genital organs (all three of these cancers were of the ovary) were all below one. In fact, only four cancers of the reproductive system were observed although 8.8 were expected based on NYC mortality rates. One brain cancer was observed compared with 1.41 expected (SMR = 0.71) and two leukaemias occurred compared with an expectation of 2.12 (SMR = 0.94).

Potential effect modifiers were evaluated for total malignancies, digestive cancers, colon cancer and breast cancer, but no significant effects were discernible (Table 6). Of interest was the finding that the breast cancer SMR was 1.22 for women treated for primary infertility compared with only 0.49 (based on two cases) for women treated for secondary infertility. Also, the SMR increased with increasing age at colon cancer death.

Cancers of the colon, ovary and breast, and NHL and leukaemia were evaluated in terms of organ doses (Table 7). Based on 15 cases, the risk of colon cancer was larger in the two higher dose categories than in the lowest one, although a trend with dose was not seen. Breast cancer was evaluated in terms of ovarian dose, assuming that ovarian function could influence breast cancer development. Among women in the two higher dose categories only three deaths occurred resulting in SMR below one. For the other cancer sites, no evidence of a radiation effect was observed.

DISCUSSION

We found no increased mortality among women with amenorrhea or hormonal infertility treated with x-radiation to the ovaries and/or pituitary gland. Indeed, there were 199 observed deaths compared to 229 expected. This deficit (SMR = 0.87) is largely due to the significantly lower than expected number of

TABLE 6 *Observed (Obs.) number of cancer deaths and standardized mortality ratios (SMR) stratified by potential effect modifiers* [a]

Potential effect modifiers	Cancer sites							
	All cancers		Digestive cancers		Colon cancer		Breast cancer	
	Obs.	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR
Age at treatment (years)								
<25	7	0.6	1	0.4	1	0.9	4	1.4
25–34	61	1.3	21	1.7	12	2.3	13	1.1
35+	10	0.9	5	1.4	2	1.4	1	0.4
Age at death (years)								
<55	15	0.8	5	1.5	1	0.7	6	1.0
55–69	43	1.3	13	1.5	6	1.6	10	1.3
70+	20	1.1	9	1.4	8	2.9	2	0.7
Type of infertility at first treatment[b]								
Primary	58	1.2	19	1.4	9	1.6	15	1.2
Secondary	17	0.9	8	1.6	6	2.8[c]	2	0.5
Parity status after treatment[b]								
Non-parous	20	1.1	7	1.4	3	1.5	5	1.1
Parous	51	1.2	18	1.5	10	2.0	13	1.2

[a] Expected number of deaths and SMR computed based on New York City mortality rates for white females, 1950–1990.
[b] Observed number of deaths do not add up to total observed deaths because of missing values.
[c] Lower confidence limit is above 1.0.

TABLE 7 *Observed (Obs.) number of cancer deaths and standardized mortality ratios (SMR) stratified by estimated organ dose*

Cancer site	Organ dose used	Median organ dose (cGy)	Dose categories (cGy)	Observed deaths and SMR by organ dose category					
				Low		Medium		High	
				Obs.	SMR	Obs.	SMR	Obs.	SMR
Colon	Average colon	45	≤45; 46–70; 71+	7	1.6	4	2.5	4	2.2
Breast	Ovary	76	≤79; 80–99; 100+	15	1.4	1	0.4	2	0.6
Ovary[a]	Ovary	76	≤79; 80–99; 100+	3	0.9	0	0.0	0	0.0
NHL[b]	ABM[c]	25	≤25; 26–35; 36+	3	2.3	2	5.7	1	2.0
Leukaemia	ABM[c]	25	≤25; 26–35; 36+	1	0.8	0	0.0	1	2.0

[a] Includes 'other and unspecified female genital organs'.
[b] NHL = non-Hodgkin's lymphoma.
[c] ABM = active bone marrow.

circulatory disease deaths. Non-significant deficits of diseases of the digestive organs, external causes, and non-specific and other causes were also noted. There was little evidence of an increased risk of cancer. Compared with age-race-sex specific NYC mortality rates, the only significant excesses were for colon cancer and NHL. In contrast, deaths from cancers of the female genital tract were lower than expected, although the difference did not reach statistical significance.

The women in this study are predominantly middle class and well educated. An inverse relationship between myocardial infarction and education and social class has been reported.[21,22] Women with higher education or social class often have a healthier lifestyle and receive better medical care than women with less economic advantages. They may exercise more, eat a lower fat diet, and control their weight better than less educated women. In addition, they frequently seek early

treatment for diseases which increase the risk of cardiovascular deaths, e.g. high blood pressure,[22] and may use postmenopausal hormone replacement therapy which is associated with about a 50% reduced risk of cardiovascular disease.[23,24] Although we do not have data on their lifestyle habits, the fact that there were no observed cancers of the buccal cavity or cirrhosis of the liver implies that the women in the study are infrequent drinkers, but their lung cancer SMR of 1.05 suggests that their smoking habits may have been closer to those of the general population. The patients in this cohort may also be at decreased risk of circulatory disease because of their low parity[22,25] and their late age at first birth.[22]

Our study provided little evidence that either infertility or its treatment with radiation increased the risk of cancer mortality overall. These results are interesting because either of these potential risk factors could affect the cancer mortality experience of the cohort. The finding that mortality from colon cancer was elevated is of note because the highest radiation exposure was to the sigmoid colon (Table 2). The median sigmoid colon dose was about 90 cGy, but ranged from 76 to 180 cGy. At these doses, radiation effects have been demonstrated among atomic bomb survivors[26] and women treated with x-rays or radium for benign gynecological diseases.[27–29] On the other hand, colon cancer risk was not elevated in two other studies of benign gynecological disease patients[30,31] or among peptic ulcer patients treated with radiotherapy.[32] At very high doses, such as given to cancer patients, the findings have been inconsistent. No excess was observed among cervical cancer patients exposed to a mean dose of about 2400 cGy,[33] but an excess was seen for ovarian cancer patients.[34] The excess relative risk (ERR) at 1 Gy was 0.67 among female atomic bomb survivors[26] and 0.51 among patients with benign gynecological diseases treated with radium.[29] Assuming a mean dose of 1 Gy to the sigmoid, our SMR of 1.90 translates into a very crude ERR estimate of about 0.9 at 1 Gy, which is within the confidence bounds of both studies.

The effect of parity also could be a factor in the excess colon cancer mortality. An inverse relationship between colon cancer and parity has been observed in several epidemiological studies.[10,35,36] In the most recent study,[10] nulliparity was associated with an odds ratio of about 1.5. Since a larger proportion of the women in this study were nulliparous than in the general population of NYC, the increased SMR for colon cancer might partly be explained by their reduced protection afforded by childbearing.

A significant excess risk of NHL was found based on six cases, but there was no evidence for a dose-response relationship. Boice[37] recently summarized the epidemiological literature and reported that an excess of NHL is rarely found subsequent to radiation exposure. Studies of atomic bomb survivors, patients receiving radiation therapy or diagnostic procedures, and exposed workers have almost always been negative. Thus, our finding does not appear to be radiation related. As noted above regarding colon cancer, it is possible that the low parity of infertile women confers an increased risk for NHL, as has been reported for Hodgkin's disease.[38]

Although the ovaries, brain and active bone marrow received direct radiation exposure, SMR for deaths due to ovarian and brain cancer and leukaemia were below one (0.58, 0.71 and 0.94, respectively). Among atomic bomb survivors, a rather large excess of ovarian cancer and leukaemia were observed at similar dose levels.[26] However, since the study population consists of only 816 people, our negative findings are statistically consistent with the atomic bomb survivor results.

Although the deficit in mortality from female genital cancers (SMR = 0.45) was not significant, it was unexpected. Previous studies have reported strong associations between nulliparity and hormone-dependent cancers, but infertility has not been reported as a significant risk factor for all cancers combined.[11–14] A link between hormonal infertility and the incidence of endometrial cancer[12,13] and ovarian cancer has been noted in several studies.[39–42] Elevated breast cancer risks were observed in some studies,[11,12,43] but they usually were confined to specific age or infertility diagnosis subgroups of the populations studied. Unfortunately, we could not determine the specific type of hormonal infertility for most patients because the records had limited clinical data and the hormonal assays used during the study period were relatively crude. It is possible that this cohort has experienced a higher rate of hysterectomy and/or oophorectomy than the general NYC population, but the low risk of cardiovascular mortality would suggest that this is not the case. Our results may also be related to the use of death certificates as the outcome variable since death certificates are not very accurate in identifying female genital cancers.[44] Finally, the findings may be due to chance alone.

In interpreting the study findings, several limitations should be noted: the size of the cohort is small and many statistical comparisons were performed; the types of infertility treatments received before radiotherapy were unknown and could not be considered in the analysis; death certificate diagnoses are frequently inaccurate and the site-specific analyses are, therefore, subject to disease misclassification; radiation exposure was generally low and the range of doses was limited;

finally the use of US national and NYC mortality data as the basis for computing expected numbers of deaths may not be appropriate for the study population. On the other hand, the follow-up rate for the study was good, the period of observation was long, and the exposure data were reliable. Overall, the data should be reassuring to women treated for infertility in years past.

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